

Management of Behavioral Symptoms in Alzheimer's Dementia

David Mansoor, MD
Associate Professor of Psychiatry
OHSU/PVAMC
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In Honor of David Lynam, MD



Conflict of Interest Disclosure

Unlabeled Use of Products:

This presentation presented by Dr. David Mansoor will discuss medicines used to treat behavioral symptoms in dementia; all medicines used to treat behavioral symptoms in dementia are off-label. The VA does not endorse the use of off-label medicines.

Overview

- Epidemiology
- Evaluation of neuropsychiatric symptoms
 - Identify target behaviors
- *Environmental and medical causes*
- *Non-pharmacological interventions*
- Medication management
 - Symptom oriented approach

Epidemiology

- Dementias can be categorized by etiology
 - Alzheimer's dementia
 - Vascular dementia
 - *Dementia with Lewy bodies*
 - Frontotemporal lobar degeneration
 - Traumatic brain injury
 - Substance induced
 - Parkinson's disease
 - Etc.

Epidemiology

- Nomenclature using DSM 5
 - “Dementia” replaced with “major neurocognitive disorder”
 - Prompted to specify the etiology
 - Major NCD due to Alzheimer’s disease
 - Major NCD with Lewy Bodies
 - Major vascular NCD
 - Major frontotemporal NCD
- I will be using the terms “dementia” and “neurocognitive disorder” interchangeably

Epidemiology

- Impairment in learning and memory
- Attentional impairment
- Loss of executive function
- Impairment in language
- Perceptual motor dysfunction
- Behavioral changes -> neuropsychiatric symptoms

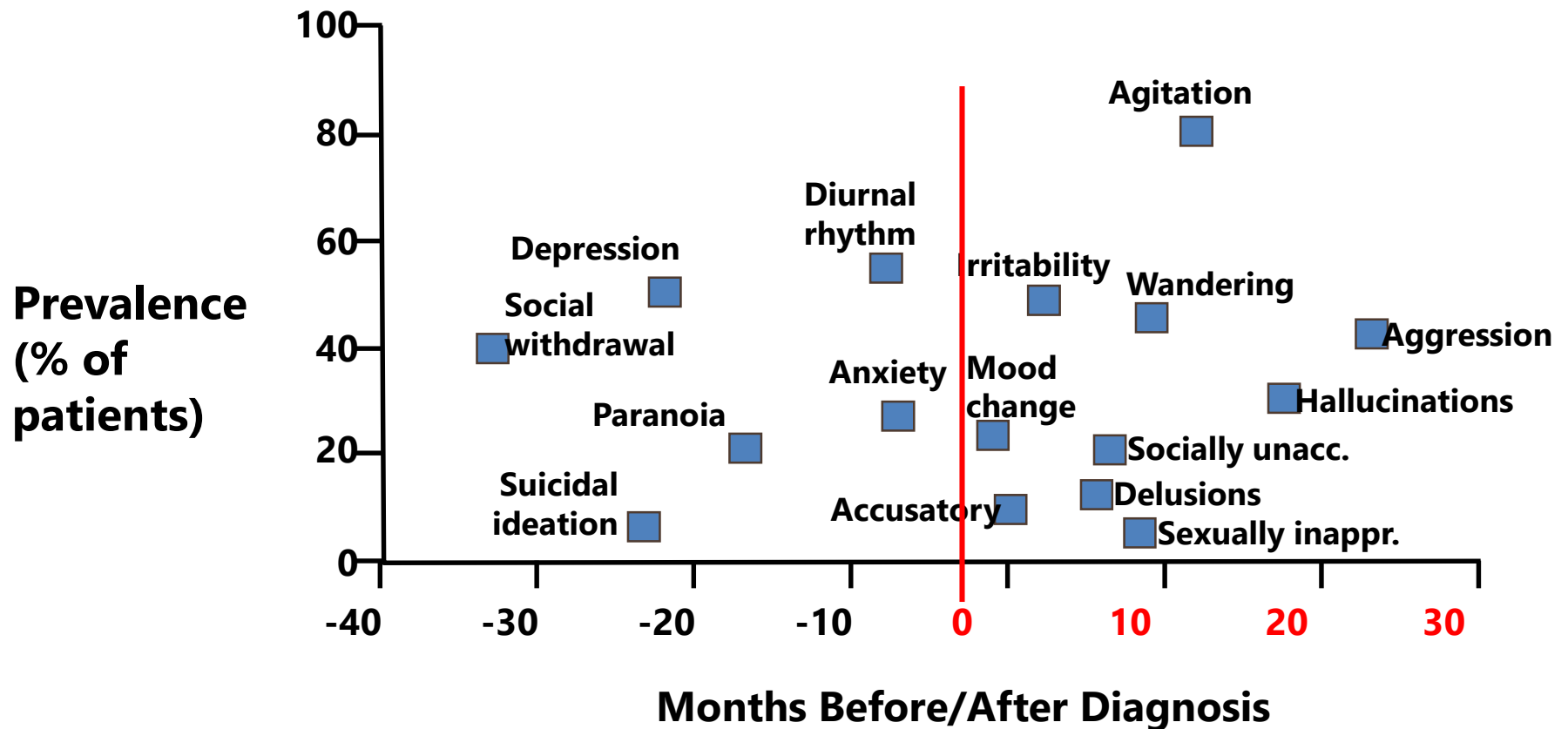
Epidemiology: Neuropsychiatric Symptoms

- Common – a central component of dementia
 - Affect up to 80% of persons with dementia
- Morbid
 - Greater impairments in IADLs, more rapid rate of cognitive decline, earlier institutionalization, greater rate of caregiver depression
- Classifiable
- Treatable

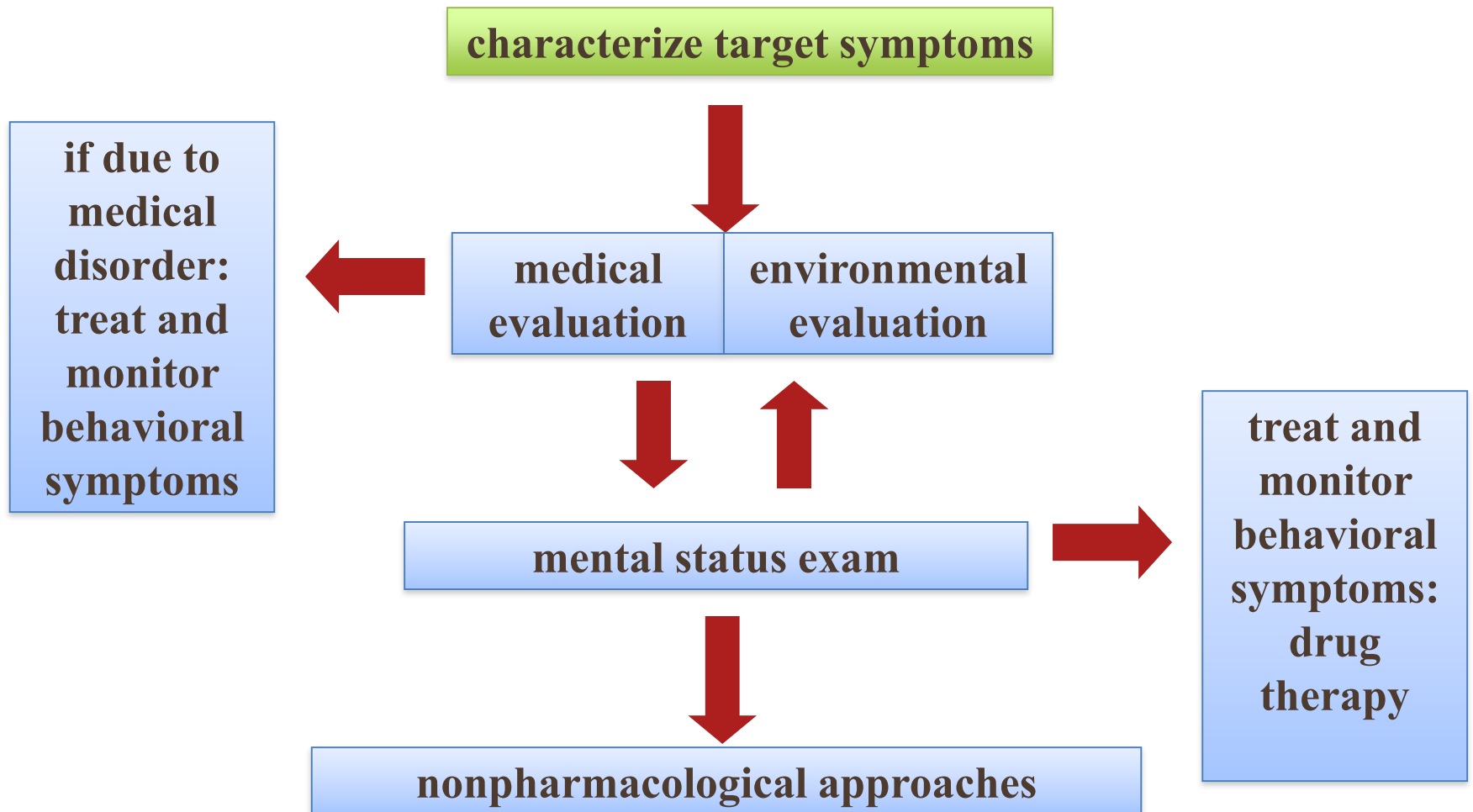
Epidemiology: Prevalence of Symptoms in Dementia

NPI Item	Dementia (n=329)	No Dementia (n=673)
	%	%
Apathy	27.4	3.1
Depression	23.7	7.0
Agitation/aggression	23.7	2.8
Irritability	20.4	4.5
Delusions	18.5	2.4
Anxiety	17.0	5.6
Aberrant motor behavior	14.3	0.4
Hallucinations	13.7	0.6
Disinhibition	9.1	0.9
Elation	0.9	0.3

Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses



General Approach to Behavioral Complications of Dementia

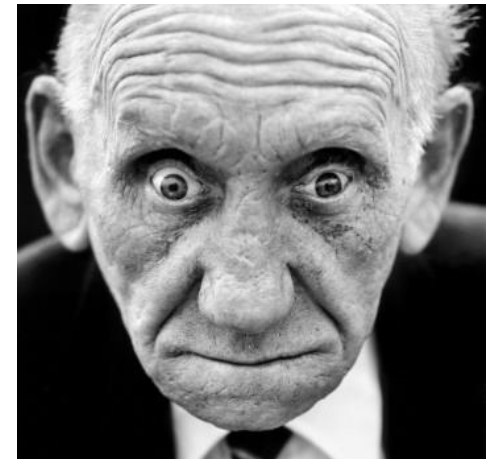


Target Symptoms

- Before any intervention it is important to understand the nature, severity, and frequency of the symptoms
 - Details are critical for directing care
- Selection of an intervention depends on the targeted behavioral symptom AND the cause

Target Symptoms: Case

- You are on call and receive a page from a care facility,
 - 82-year old patient with advanced Alzheimer's disease who has been at an adult foster home for 2 years
 - “He is sundowning. We need something to calm him down.”
 - “he is agitated”



Target Symptoms: Case

- “Agitation” is commonly used
 - It is nonspecific
 - It is not a diagnostic term
 - No universal definition
 - Variably used: typically assigned by an observer depending on whether *they think* the behavior seems appropriate
 - Doesn't help you to establish cause / severity / safety
- A more precise description can assist with identifying the underlying cause and selection of effective interventions
- Define target behavior

Target Symptoms

- Aggressive
 - Physical
 - Verbal
- Nonaggressive
 - Physical
 - Verbal

Target Symptoms

- **Physical aggression:** hostile acts directed toward others, self, or objects
 - Hitting, kicking, biting, grabbing, scratching, spitting, hurting self or others, destroying property, physical sexual advances
 - *Tend to occur in later stages*
 - Often during times of close contact
 - More common in men than women

Target Symptoms

- **Verbal aggression:** temper outbursts, making strange noises, screaming, cursing, threatening, accusing, name calling, verbal sexual advances

Target Symptoms

- **Physical nonaggression**
 - Repetitive mannerisms, general restlessness, wandering, pacing, disrobing, trying to get to a different place, hiding, hoarding
- **Verbal nonaggression**
 - Complaining, repeating words and sentences, constant talking, strange noises, calling out

Target Symptoms

- Rating scales can be very helpful, and are recommended by the APA
 - Cohen Mansfield Agitation Inventory
 - 29-item scale
 - Caregiver rates frequency of behavior over prior 2 weeks
 - Neuropsychiatric Inventory Questionnaire
 - 12-item scale
 - Caregiver rates presence/absence of behavior, severity (mild/moderate/severe), level of distress over prior month

Target Symptoms

- Helps to understand etiology
 - *Wandering*: looking for home? looking for bathroom? anxious? akathisia? understimulated?
 - *Verbal repetition*: sensory deprivation? confusion? hunger? thirst?
 - *Aggression*: psychosis (delusion, hallucination)? fearful? in pain?

Target Symptoms: Case

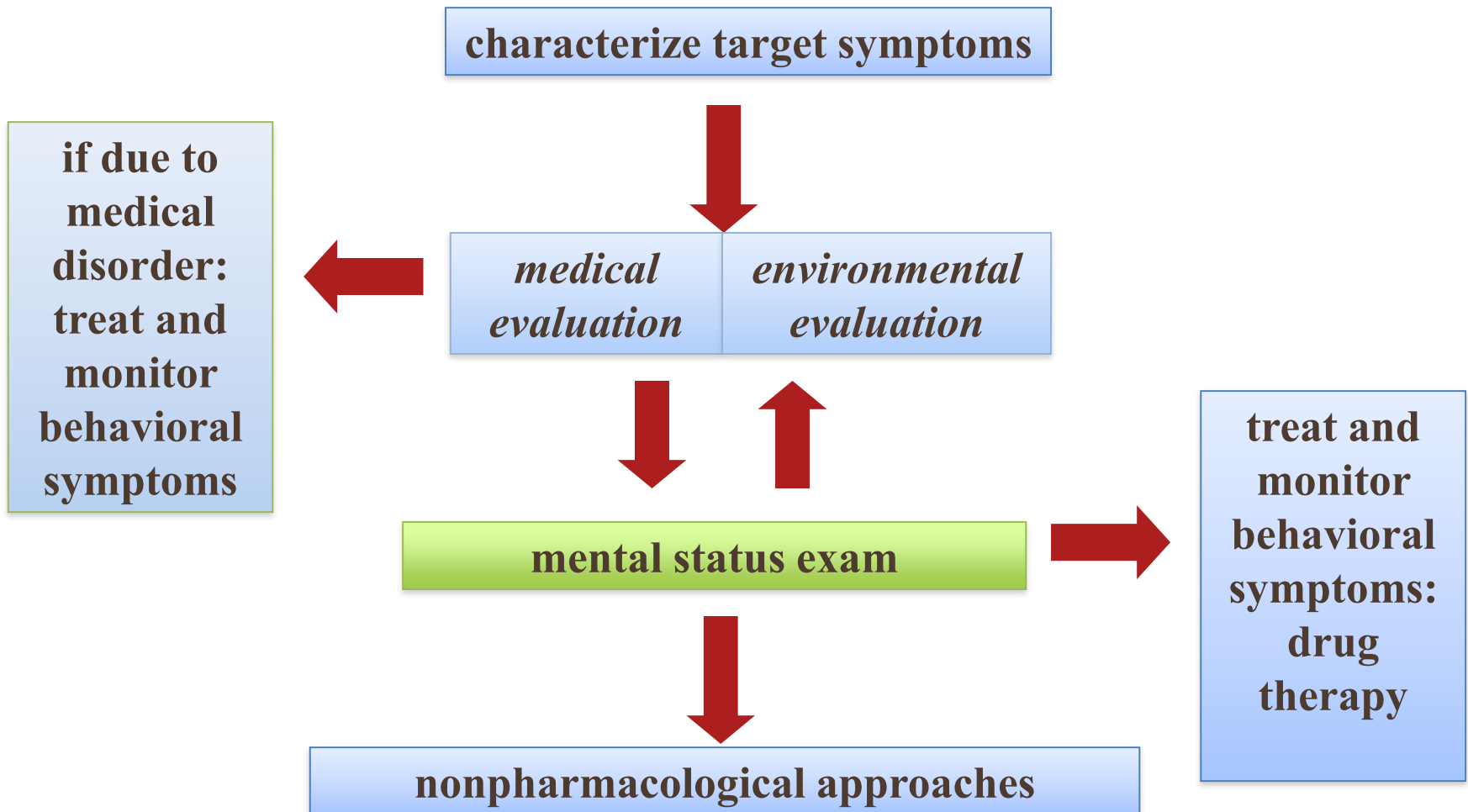
- At a clinic visit, a caregiver says your patient Mrs Y is having “hallucinations”
- She is a 75-year old with moderate Alzheimer’s disease who lives at home



Target Symptoms: Case

- Define the target behavior / symptom
 - “what do you mean by hallucination?”
- Hallucinations?
 - Auditory?
 - Visual?
- Delusions?
 - Paranoid?
 - Spouse having an affair; stealing; others in the house
 - Misidentification? (eg, spouse isn't their spouse)

General Approach to Behavioral Complications of Dementia



Evaluation: Mental Status Exam

- General appearance:
 - Grooming? Weight? In pain? Level of consciousness?
- Behavior
 - Cooperative? Uncooperative?

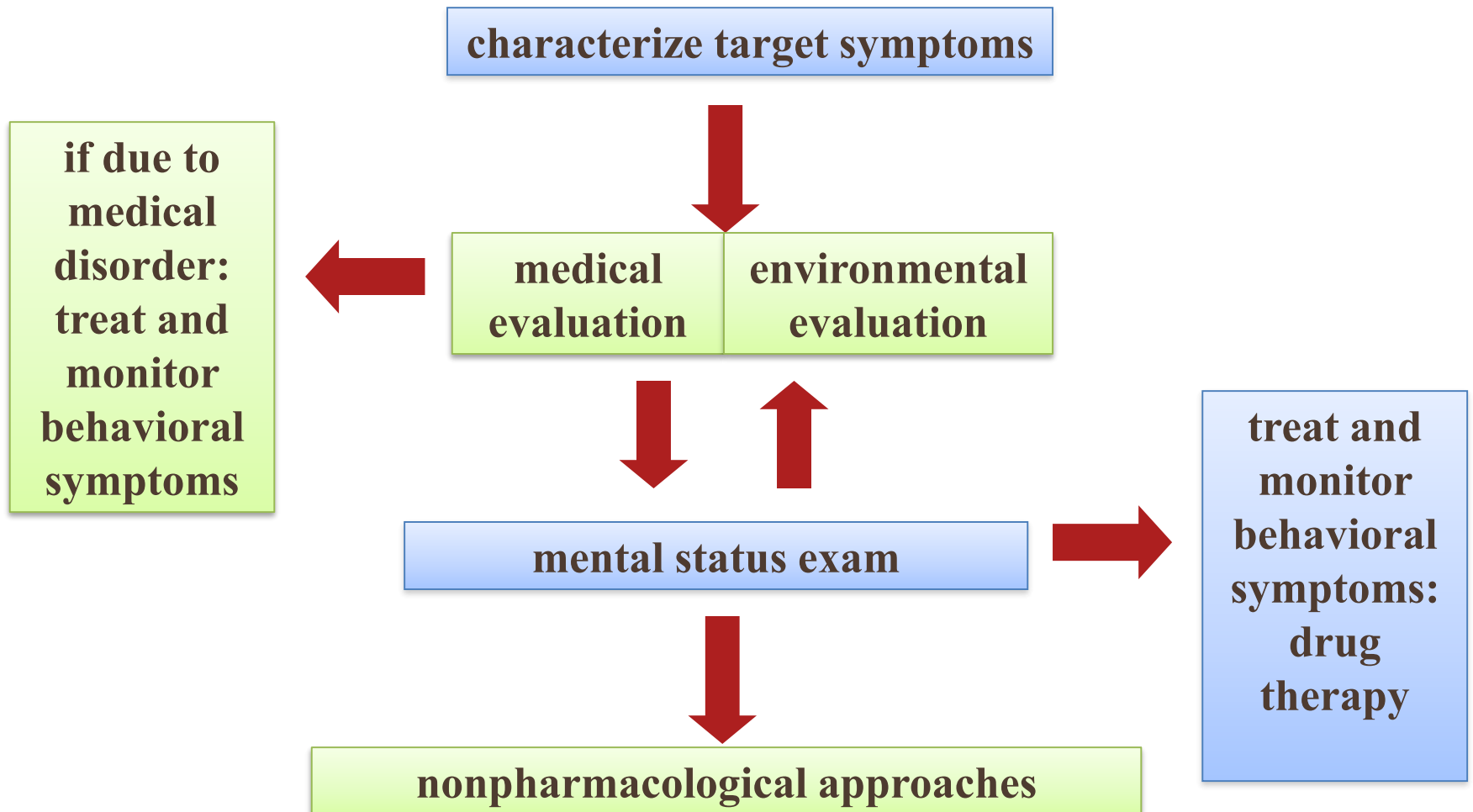
Evaluation: Mental Status Exam

- General appearance:
 - Grooming? Weight? In pain? Level of consciousness?
- Behavior
 - Cooperative? Uncooperative?
- Speech/Language
 - Quantity? Smooth/effortless or halting?
 - Word finding difficulty → General use-phrases (“that thing,” “you know what I mean”) → loss of meaningful content → comprehension difficulty → dysarthria / mutism
- Mood
 - “How are your spirits today?”
- Affect
 - Anxious? Depressed? Blunted? Fearful?

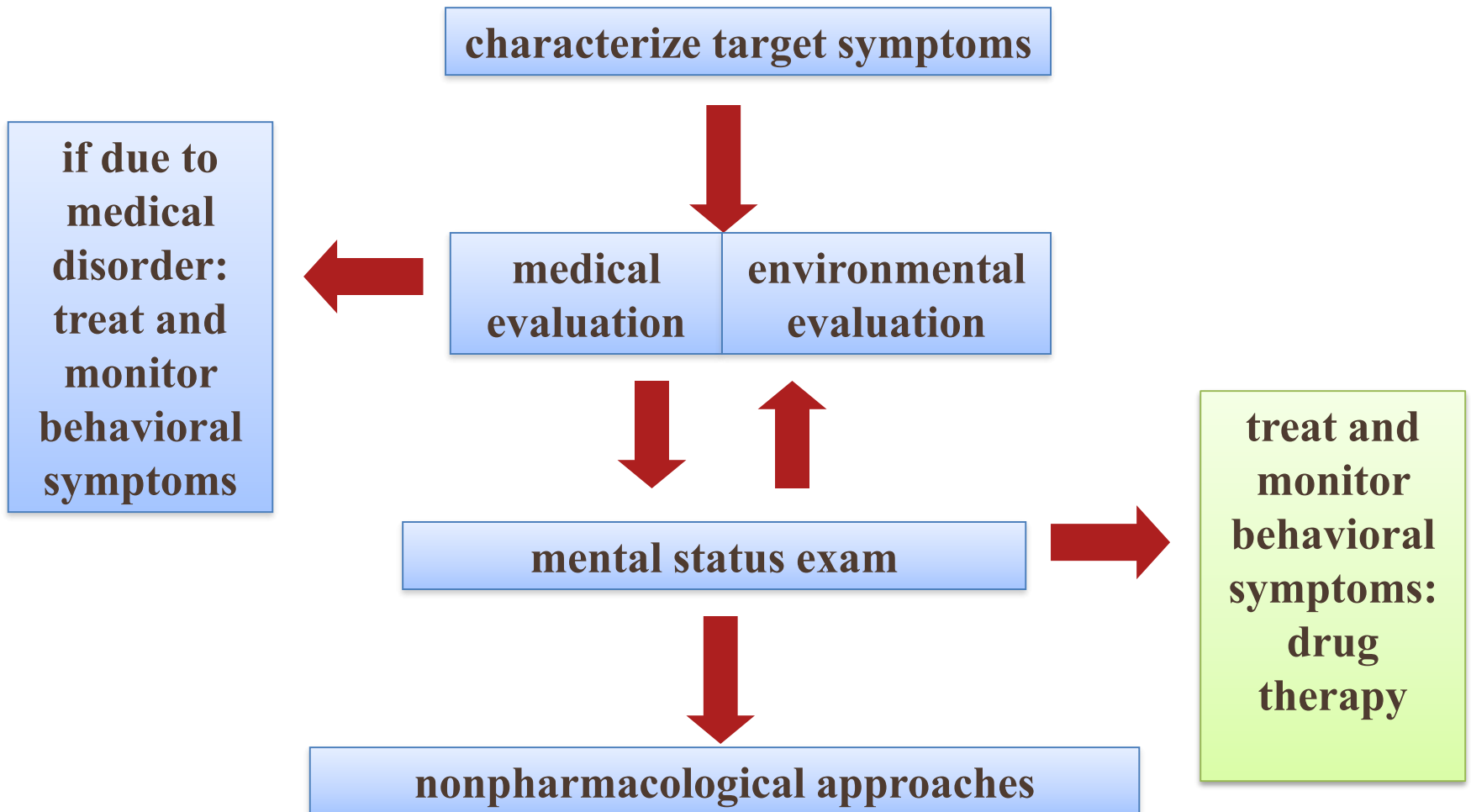
Evaluation: Mental Status Exam

- Thought process
 - Organized with circumlocution (word retrieval) -> tangential-> disorganized
- Thought content
 - Delusional? Hallucinations? Suicidal thoughts?
- Insight
 - Anosognosia?
- Cognition
 - 30-pt mental status exam (eg, SLUMS)
 - Establish baseline and how far off from baseline?
 - Imbalances across tasks specific to cognitive domains

General Approach to Behavioral Complications of Dementia



General Approach to Behavioral Complications of Dementia



Pre-Prescribing Considerations

- There are no FDA approved medications for treating behavioral symptoms due to Alzheimer's dementia
- There is no magic bullet
- Typically need a combination of behavioral intervention and pharmacotherapy

Pre-Prescribing Considerations

- Psychotropic medicines were developed for younger generally healthy adults without dementia
- When using a medication, do so judiciously, in the lowest effective doses, and for the shortest period necessary
 - Start low and go slow (but go!)
- Age related physiologic change -> more susceptible to side effects

Pre-Prescribing Considerations

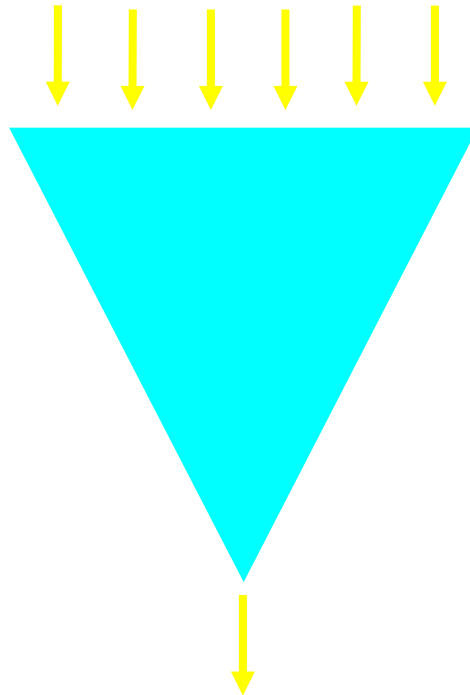
- Ineffective medications should be stopped
 - “Can the behavior be any worse off this medication?”
- Consideration should be given to periodic trial dose reductions of effective medications to learn whether treatment is still necessary

SYMPTOM ORIENTED APPROACH

Symptom Oriented Approach

Traditional Approach

Signs and
Symptoms



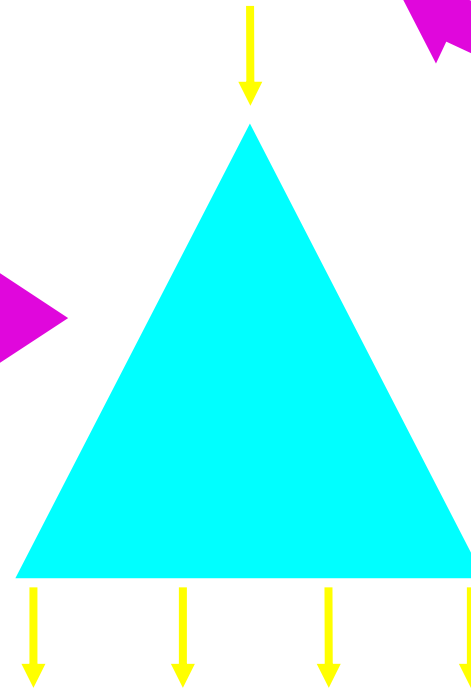
Pneumonia

Treat



Symptom Approach

Symptom



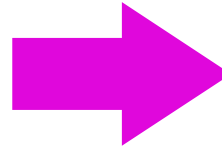
AD

DLB

TBI

Vascular

Treat
(e.g.,
“psychosis”)



Symptom Oriented Approach to Treatment

- Define the target behaviors
- Look for a pattern in the patient's target symptoms analogous to what is seen in a "*drug responsive*" psychiatric syndrome
- **Psychotic** – suspicious, angry when approached, delusional
- **Depressive** – irritable, sad, vegetative, withdrawn, tearful
- **Manic** – impulsive, accelerated, hypersexual, labile affect
- **Anxious** – worry, restless, somatic concerns, calling out

Symptom Oriented Approach to Treatment

- Match the target symptom to the drug class

Behavioral disturbance	Drug to consider
Depressive	Antidepressant
Psychotic	Antipsychotic
Manic	Mood Stabilizer
Anxiety	SSRI

TREATMENT BY DRUG CLASS



**“Each capsule contains your medication,
plus a treatment for each of its side effects.”**

Considerations

- Multiple classes of psychotropic medication have demonstrated efficacy in treating behavioral symptoms
 - Antidepressants
 - Mood stabilizers (Valproate preparations)
 - Cholinesterase inhibitors / Namenda
 - Antipsychotics

Antidepressants

Antidepressants - Agitation

- Often used because well tolerated and have few serious side effects
- Few studies of antidepressants for the treatment of agitation in dementia
- Most studies are small and did not control for depressive symptoms
- Agitation symptoms **vary** across studies, methodologic differences

Antidepressants - Agitation

- Cochrane Review 2011, antidepressants for agitation in dementia (various dementias):
 - The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies
 - Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotic
- Antidepressants such as citalopram, sertraline, and trazodone **may improve** symptoms of agitation for some individuals with dementia
- Given the tolerability and safety of these medications they **may be considered** as a potential treatment for agitation

Antidepressants - Agitation

- APA Practice Guidelines (2007)
 - “A therapeutic trial of trazodone, buspirone, or an SSRI may be appropriate for some nonpsychotic but agitated patients, especially those with relatively mild symptoms or those who are intolerant of or unresponsive to antipsychotics”
 - Guideline Watch Update (2014)
 - New evidence from a single trial suggests benefits for citalopram in the treatment of agitation in patients with Alzheimer’s disease
 - CitAD: 9wk RCT psychosocial intervention + citalopram (n=94) or placebo (n=92)
 - Addition of citalopram reduced agitation and caregiver distress
 - Citalopram titrated to 30mg*

Antidepressants - Depression

- APA Practice Guidelines (2007)
 - “Although evidence for antidepressant efficacy in patients with dementia and depression is mixed, clinical consensus **supports a trial** of an antidepressant to treat clinically significant, persistent depressed mood.”
 - “The choice among agents is based on the side-effect profile of specific medications and the characteristics of the individual patient. SSRIs may be preferred because they appear to be better tolerated than other antidepressants. Bupropion, venlafaxine, and mirtazapine may also be effective.”
- APA Practice Guidelines Watch (2014)
 - “Clinical consensus **still supports** undertaking one or more trials of an antidepressant to treat clinically significant and persistent depressed mood in patients with dementia.”

Antidepressants

- Use for apathy, depression symptoms, or agitation driven by depression
- Start low and go slow
 - Escitalopram: 2.5mg titrated to 10mg
 - Sertraline: 25mgm titrated to 100mg
 - Citalopram, 5mg titrated to 20mg
 - Mirtazapine, 7.5mg titrated to 30mg
 - Low dose trazodone (12.5-25mg) up to tid
 - Avoid older tricyclics (amitriptyline, imipramine, etc), paroxetine, fluoxetine, fluvoxamine

Antidepressants – Side Effects

- Constipation
- Diarrhea
- Nausea
- Dizziness
- Dry mouth
- Falls
- Nervousness/akathisia
- Headache
- Tremor
- Decreased libido
- Gait instability
- Fatigue
- *Hyponatremia*¹
 - Up to 12% (paroxetine)

1, Fabian TJ, Amico JA, Kroboth PD, et al. Paroxetine induced hyponatremia in older adults: a 12-week prospective study. Arch Intern Med. 2004;164:327-332.

Cognitive Enhancers: Cholinesterase Inhibitors and Memantine

Cholinesterase Inhibitors

- Increase Ach in the synaptic cleft
 - May delay cognitive and functional decline
- Galantamine, Rivastigmine, Donepezil
- 2009 Systematic Review (14 RPCTs, AD)¹
 - NPI scores, apathy scales, agitation scales
 - Results were mixed: at best “modest” impact on a broad spectrum of behavioral symptoms
- Generally well tolerated and worth trying if symptoms are mild or if risks of other medications are high

1. Rodda J. Are Cholinesterase Inhibitors Effective in the Management of Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease? International Psychogeriatrics. 2009.

Cholinesterase Inhibitors

Adverse effects

- Cardiac
 - Bradycardia
 - AV Block
 - Syncope
 - QT prolongation
- GI
 - Peptic ulcer
 - Nausea
 - Vomiting
 - Diarrhea
- CNS
 - Seizures
 - Agitation
 - Hallucinations
 - Confusion

Drug interactions

- Bupropion
- Anticholinergics
- Beta blockers
- NSAIDs
- 2D6 inhibitors (paroxetine, fluoxetine) increase levels of galantamine and donepezil

Memantine

- Memantine (Namenda)
 - Binds NMDA receptor, inhibits influx of Ca^{2+} ions, reduces glutamate induced neuronal toxicity
 - Indicated for moderate to severe Alzheimer's
 - Literature is also mixed and limited
 - Most studies recruited patients for the purpose of testing cognition, not behavioral symptoms
 - Generally well tolerated, with cognitive and functional benefit in patients with moderate to severe dementia, worth trying if behavioral symptoms are mild
 - Side effects: dizziness, confusion, vivid dreams, hallucinations, agitation, headache

Mood Stabilizers

Valproate Preparations

- Not recommended by APA¹ or Cochrane Review²
- Anecdotal reports abound along with positive open label studies
 - Effective in a broad range of psychiatric conditions characterized by agitation
 - “...a therapeutic trial may be considered in individual cases, for example, in patients who are sensitive or unresponsive to antipsychotics, who have significant vascular risk factors, or who do not have psychosis but are mildly agitated”
- Can be easier to administer than a pill
 - Available in liquid and “sprinkles”

1. Rabins et al. APA Guideline Watch Practice Guideline for the Treatment of Patient's with AD and Other Dementias. 2014
2. Baillon et al. Valproate preparations for the treatment of agitated behaviour in people with dementia. *Cochrane Database Syst Rev*. 2018

Valproate Preparations

- Consider for aggressive / impulsive behavior in the absence of psychotic symptoms or mood lability without response to other medications
 - Dose low
 - Start 125mg bid
 - Rarely exceed 1000mg per day
 - Use delayed or extended-release formulation
- Side effects: sedation, GI upset, tremor, hepatitis, thrombocytopenia
- Monitoring: LFTs, CBC

Antipsychotics

Antipsychotics

- May increase mortality and stroke
 - FDA Black Box Warning (2005)
 - 1.7-fold increase in mortality compared with placebo (4.5% vs 2.6%)
 - Risk higher for 1st generation antipsychotics^{1,2}
 - Olanzapine > risperidone > quetiapine²
 - May be dose dependent²
 - Risk persists³

1. BMJ 2012; 344.
2. J Am Geriatr Soc 58:1027–1034, 2010
3. Ballard et al. 2009).

Antipsychotics

- Benefits often still outweigh the risks in patients when treatment of psychosis and physical aggression is critical
 - Individual risk/benefit analysis

Antipsychotics

- Typical Antipsychotics, Haloperidol
 - Cochrane Review 2002¹
 - Haloperidol was useful in the control of aggression/hostility/suspiciousness
 - “There is little evidence to support a benefit of haloperidol on manifestations of agitation other than **aggression**”
 - Adverse effects more common than placebo
- Atypical Antipsychotics
 - Cochrane Review 2006²
 - Risperidone 1-2mg and olanzapine 5-10mg improved aggression compared to placebo
 - Risperidone improved **psychosis** relative to placebo

1. Loneragan E, Luxenberg J, Colford JM, Birks J. Cochrane Database of Systematic Reviews 2002

2. Ballard C, Waite J. Cochrane Database of Systematic Reviews 2006

Antipsychotics

- APA Practice Guidelines: “nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient”
 - Risks and benefits from antipsychotic medication should be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient’s surrogate decision maker (if relevant) with input from family or others involved with the patient

Antipsychotics

- If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn
- If there is an adequate response of an attempt to taper and withdraw the drug should be made within 4 months of initiation

Antipsychotics

- No clear difference in efficacy between drugs
- Most used
 - Olanzapine: 2.5mg (start) up to 10mg
 - Quetiapine: 25mg (start) up to 150mg
 - *Least EPS risk, dosing flexibility, helps sleep*
 - Risperidone: 0.5mg (start) up to 3mg
 - Haloperidol: 0.25mg (start) up to 3mg

Antipsychotics

- Side effects: EPS, orthostasis, akathisia, somnolence, *falls*, metabolic, cerebrovascular events, upper respiratory tract infection, cardiac events, tardive dyskinesia
- Avoid in dementia with Lewy bodies!!!
 - Start with a CI
 - Minimize dopaminergic drugs
 - Use quetiapine if an antipsychotic is needed

Other: Benzodiazepines,
Diphenhydramine, Prazosin,
Pimavanserin,
Dextromethorphan/Guanfacine

Benzodiazepines and Diphenhydramine

- Benzodiazepines
 - Minimal data supporting efficacy
 - Sedation, falls, cognitive impairment
 - Avoid
- Diphenhydramine
 - Common OTC sleep aid (inquire about Tylenol PM)
 - Anticholinergic
 - Sedation, falls, cognitive impairment
 - Avoid

Prazosin, Pimavanserin, Dextromethorphan/Quinidine

- Prazosin
 - DBRPCT, 22 nursing home and community dwelling patients with AD
 - Prazosin 1-6mg vs placebo
 - Assessed over 8 weeks (only 54% completed), NPI
 - Prazosin (mean dose 5.7mg) was well tolerated and improved behavioral symptoms
 - Very small study, high drop out rate, no sub-item statistical analysis
 - Conclusion: Reasonable to try but not as first line therapy

Dextromethorphan/Quinidine

- Nuedexta
 - DBRPCT, 220 patients with probable AD, mostly outpatients
 - Stage 1: placebo vs Neudexta
 - Stage 2: placebo rerandomized to placebo vs Neudexta
 - Assessed over 10 weeks, NPI agitation/aggression domain
 - Nuedexta improvement in agitation scores
 - Higher rates of falls and UTIs
 - Pharma designed and funded, patented study design prevents replication and validation; conflicting results from larger phase 3 studies in 2019
 - Conclusion: okay for PBA, but not agitation in dementia

Pimavanserin

- Nuplazid:
 - Atypical antipsychotic
 - Inverse agonist and antagonist at the 5HT_{2A} receptor
 - Results from Phase 3 Harmony study submitted to FDA for supplemental drug application
 - Relapse prevention study, 392 patients with dementia psychosis
 - 12-week open label pimavanserin treatment period; responders randomized 26-week DBPC period
 - Reduced risk of relapse in patient on pimavanserin
 - Pharma funded, study results not yet published
 - Conclusion: TBD, study design doesn't tell you who to start on pimavanserin

Hypnotics for Sleep

Hypnotics

- Try to implement non-pharm interventions
 - Melatonin: dose 1mg – 6mg qhs
 - Trazodone: start 25mg qhs, dose up to 100mg
 - Mirtazapine: consider if there are coexisting mood or anxiety symptoms, start 7.5mg qhs
 - Magnesium 150mg – 200mg qhs
-
- Do not use antipsychotics solely as hypnotics
 - Do not use hydroxyzine, Benadryl, or benzos!

Summary

“Pearls”

- Use data to formulate a hypothesis of cause of behavior
- Start with nonpharmacological approaches
- Reserve pharmacotherapy for behaviors that are severe, persistent, and/or resistant to nonpharmacological treatments

“Pearls”

- If monotherapy fails, use judicious combination of medications (eg, avoid using medicines from the same drug class)
- If lots of medications do not help, start discontinuing medications
 - Can they be any worse off medications?

“Pearls”

- Less-severe behaviors with limited consequences of harm to individual or caregiver, avoid using antipsychotics
- More severe or “high risk” behaviors such as frightening hallucinations, delusions or hitting may require addition of antipsychotic trial

The End

email me: mansoord@ohsu.edu

Evaluation – Medical

- Discomfort / Pain
 - Musculoskeletal, constipation, urinary retention, hunger, thirst
- Review vital signs
 - Assess for infection, weight change, autonomic changes
- Medications
 - Benzodiazepines, opiates, anticholinergics, antihistamines

Evaluation – Medical

- Basic labs as indicated
 - CBC, chemistry panel, TSH, b12
 - Urinalysis for UTI symptoms
- Imaging only as indicated
 - New neurologic finding
 - Recent fall with mental status change, headache, neurologic findings

Evaluation - Environment

- Environment
 - Over stimulating?
 - TV, telephone, visitors, mirrors, pictures...
 - Under stimulating?
 - Dark, quiet, reduced sensory input
 - Unfamiliar
 - Transitions and changes in routine can be disruptive

Non-Pharmacological Approach

- Develop a structured daily routine
- Offer daytime recreational therapy
- Increase physical activity during the day and avoid napping
- Create a quiet and comfortable sleep environment
- Weighted blanket
- Limit evening fluid intake, empty bladder
- Bright light during the day and darkness at night
- Avoid caffeine, alcohol, nicotine

Non-pharmacological Approach

- Bathing: make bathroom safe, comfortable room and water temp, don't rush, wash hair last, towel bath
- Dressing: limit choices, prepare clothing, large clothing and soft stretchy fabric, Velcro shoes
- Eating: maintain regular mealtime, avoid distraction, check food temperature, finger foods, sweeten foods,

Non-pharmacological Approach

- Wandering: provide adequate daily physical activity, create safe wandering paths, remove reminders of leaving (coats, umbrellas), alarms or bells at door exits, ID bracelet
- Incontinence: schedule voiding, nonverbal cues (pacing), put signs at the bathroom door, clear obstacles
- Delusions: avoid challenging